

## The Coevolutionary Relationship of Humans and Domesticated Plants

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**ABSTRACT** Human-plant interactions have figured prominently in our species' evolution and they continue to influence the contemporary geographical patterns of human biodiversity. The domestication of particular plant taxa has genetically modified those taxa and intensified human contact with specific plants and their endogenous bioactive allelochemicals (secondary plant compounds). This contact, sustained over multiple generations of humans and plants has provided, on occasion, unique opportunities for amplified interactions of microevolutionary importance. In this paper, a theoretical overview of these interactions is presented and four case studies are detailed as examples of local potentially coevolutionary specificity. The first set of case studies include two human-plant diads: 1) salivary proline-rich proteins and carcinoma in East Asian ethnic groups and ingestion of tea (*Camellia sinensis*) flavonoids (polyphenols) and 2) HLADQ2+ phenotypes and celiac disease in Northern Atlantic European ethnic groups and ingestion of wheat (*Triticum aestivum*) A-gliadin peptides. Since established human-plant interactions frequently involve a third species, the second set of case studies includes two human-plant-parasite triads: 1) red blood cell G6PD variants similar to Gd<sup>med</sup> and favism in Mediterranean ethnic groups and ingestion of fava bean (*Vicia faba*) glycosides and exposure to *Plasmodium falciparum* malaria and 2) Hb $\beta$ S phenotypes and sickle cell anemia in West African ethnic groups and ingestion of cassava (*Manihot esculenta*) cyanogenic glucosides and exposure to *Plasmodium falciparum* malaria. © 1996 Wiley-Liss, Inc.

The rationale for the systematic study of the reciprocal interactions between humans and plants is well-grounded in biological anthropology. Human survival and evolutionary change has always been contingent upon successful interactions between hominids and other life forms. These interactions have shaped the biology and behavior of each participating species in ways that we are just beginning to identify, quantify, and understand. However, in spite of the relevance of human-plant interaction studies to understanding the process of human diversification and the geographical patterns of human

variability, research in this area is still at a very early stage of development.<sup>1</sup>

This paper is in two parts: Part one focuses on the theoretical premises for biocultural evolutionary ecology and the potential for human-plant coevolution. Part two dis-

<sup>1</sup>In fact, the only other published article specifically dealing with coevolution in humans is Budiansky's (1994) paper on the coevolution of humans and domesticated animals. This paper was presented at the 1993 American Veterinary Medical Association Animal Welfare Forum. Most coevolutionary studies have discussed insect-plant interactions, plant-pathogen interactions, and more recently, mammalian herbivore-plant interactions.

cusses four case studies of reciprocal interactions between specific human groups and particular plant species. These four case studies include two examples of human-plant diads and two examples of human-plant-parasite triads. In each of these multispecies interactions each group is seen as having adapted to selection pressures imposed by the other. However, since our orientation is bioanthropological, the impact of these plants on human biology and behavior is emphasized.

## THEORETICAL FOUNDATIONS

### The interface of human biology and human culture

Humans are biocultural organisms. This infers that many aspects of human biology (e.g., physiochemistry) and human culture (e.g., diet-associated behaviors) are interwoven and reciprocally influential. Indeed, some critical aspects are indistinguishably linked. In certain cases, the interactions are so tightly meshed that it is difficult to meaningfully distinguish the exclusively biological or cultural aspects of their interface. It is in this context that an integrated, biocultural analysis is most informative.

The biocultural product of the intense interactions between human biology and human culture is an infinite product. Most biocultural products are the result of an unlimited number of factors that may either converge or oscillate over time, depending upon the status of the biological and cultural factors contributing to the product subunits and the ecological context within which the subunits interact and the product is expressed. The biocultural product is an interactive whole whose integrity is a function of the fit, at various tropic levels, of its subunits.

Human biology and behavior, including cultural behavior, are dynamic components of ecology and hence are subject to selection and are capable of directional change over time. This premise has been a working assumption in biological anthropology, particularly among human biologists. However, researchers and theoreticians in this area have been largely remiss in providing biologically precise and socioculturally accurate exam-

ples of this premise. So while the biocultural perspective has been a central component of bioanthropological thinking, only a handful of genuine examples of biocultural interactions have been quantified and elaborated. Part of the problem has been the utter complexity of most biocultural products. Most bioanthropologists have been trained scientifically in reductionist techniques. By breaking down the product into smaller, more tractable parts we hope to gain insight into the connections between product subunits. The limitations of this approach in fully understanding infinite products is obvious: the sum of the parts do not necessarily equal the whole. The optimal research approach may be a synthesis of *reductionist strategies* targeted at understanding in detail the characteristics of each subunit of a biocultural product and *assembly strategies* aimed at understanding the potential and actual interactions of the product subunits *within the appropriate ecological context*.

The importance of having detailed information on biocultural product subunit data (from both biological and cultural sources), conducting an integrated analysis, and then placing these results within the appropriate ecological context cannot be overemphasized. Take the following case as an example. It was once proposed, based upon a detailed analysis of the literature, that the annual consumption of yams (*Discorea rotundata* and *Discorea cayanensis*) among Kwa speakers in West Africa (primarily Nigeria) was correlated with the frequency of sickle cell hemoglobin (Hb $\beta$ S) (Durham, 1983). Theoretically this appeared to be a plausible example of a biocultural interaction: yams, well known staples in Southeast Asia, West Africa, Papua New Guinea, and Ethiopia (Norman et al., 1984), contain saponins (Oakenfull and Sidhu, 1989). These glycoside compounds are definitely bioactive in humans, causing hemolysis of red blood cells, and the potential for an interaction between yam allelochemicals and West African human biology was plausible. On closer analysis, however, imprecision in the literature as to what was identified as yams, confusion of this plant with cassava (*Manihot esculenta*) and other roots by nonindigenous informants, and an absence of precise data

on the intake loads of these allelochemicals among West African consumers with and without Hb $\beta$ S all contributed to the untimely demise of the hypothesis. The biocultural product remains to be adequately studied. Increasingly, the prerequisite for bioanthropologists interested in identifying and understanding the interactions comprising a biocultural product will be experience in and data from both the field and the laboratory. Only then can coevolutionary hypotheses be adequately tested and biocultural adaptations identified.

### **Coevolution in human evolutionary ecology**

The term coevolution has been used by many authors in diverse and sometimes contradictory ways. In regular use since the early 1960s (Spencer, 1988), the meaning of the term coevolution continues to change as our knowledge of multispecies interactions improves. In a sociobiological context, coevolution has been applied to the interrelationships of human genes and culture (e.g., Lumsden, 1988; Durham, 1991). Some molecular biologists have used coevolution to discuss interactions between genes within a single species (e.g., Schwaiger et al., 1993). In this paper, however, the term is restricted to its classical ecological definition although the focus is still on processes rather than endpoints. Coevolution here refers to some form of reciprocity of evolutionary significance between two or more nonoverlapping species. Applied to humans, coevolutionary interactions may range in intensity, or perhaps more accurately stated, they may range in our ability to measure the depth of coevolutionary interactions. Interactions may be so precise, so tightly fitting that they involve identifiable reciprocal gene-for-gene changes in participating local groups (e.g., Leonard, 1994). At the other extreme, coevolutionary interactions may appear, at this stage in our technology and insight, to be more nebulous, involving more general reciprocal phenotypic effects in participating local groups.

In *The Coevolutionary Process*, Thompson (1994) emphasizes that the coevolutionary process both requires and produces some degree of specialization within biological com-

munities. Humans impose often profound directional selection on plant populations through the process of domestication. Bioactive plant allelochemicals (secondary compounds and their metabolites) are capable of influencing the physiological status and biological fitness of individual humans and groups. The latter group effect is a function of the extent to which plant-contact patterns are generalized within a cultural group since plant contact is modulated by cultural practices. A majority of human-plant contacts are associated with the production and consumption of food. The evolution of food products, like that of living organisms and other systems, is a nonlinear process (Peleg, 1994). Redundancy in dietary choices within a cultural group predisposes the group to the bioactive effects of plant compounds. Indeed, specific dietary preference may be a central part of a cultural group's identification and self-definition. Hence, group-level effects of particular patterns of exposure to plant products are amplified by cultural predilections that increase behavioral uniformity within the group and magnify differences between cultural groups. This asymmetry in human biocultural responses to specific plants contributes to the geographical mosaicism observed in contemporary human biodiversity, discussed later in this paper. This asymmetry in response across geographical space or environmental gradients also allows human biologists to begin to discern local patterns of specialization in particular human-plant relationships and to ascertain the extent to which they may be coevolutionary.

### **Historical context of human-plant interactions**

The foundations of contemporary human plant use are in our species' evolutionary past, among the early hominids forms that anatomically resemble modern humans, and even further back in time among the primate precursors to these forms. Early events in primate history may have contributed to contemporary human biological baselines. For example, adequate regular intakes of plant-derived vitamin C millions of years ago may account for current human deficiencies in L-gulonogamma-lactone oxidase, a key

enzyme for L-ascorbic acid biosynthesis. Consistent primate-plant interactions in the past may have obviated the need for endogenous vitamin C synthesis in fruit-consuming primates. The conservative physiochemical response to regular and reliable supplementation may explain why sequence analysis of the human L-gulonolactone oxidase pseudogene reveals that its current inactivity is accompanied by a large number of accumulated mutations (Nishikimi and Yagi, 1991). Dietary changes in the patterns of exposure to plant based compounds continue to lead to alterations in key metabolic processes in consuming individuals and groups. These effects exhibit direct effects of the genome by altering gene function and expression of the phenotype (Hargrove and Berdaniel, 1992). For example, the micronutrients zinc and magnesium have been shown to interact directly with the mammalian genome, modifying transcription regulation and chromatin structure (Castro et al., 1986; Cousins, 1989).

Differences in plant use among australopithecines likely accounts for species variation in tooth size, shape and surface morphology among *Australopithecus* and *Paranthropus* (Grine, 1987). These dietary differences are also thought to imply other taxonomically important distinctions, for example, differences in cognition. In the absence of tools, tooth size, shape, and surface microwear patterns reflect dietary choice during the lives of these early bipeds. Plants figured prominently in the diets of both genera and regular exposure to plant products continued with the subsequent emergence of the genus *Homo*. In fact, regular tool manufacture and use further expanded the accessibility of plant-based foods for early humans. The generalist feeding strategy of modern humans is rooted in the gathering and hunting mode of life. This mode has been our species' traditional occupational niche and the gathering of plant foods has been the central, most consistent theme of human subsistence (cf. Zihlman and Tanner, 1978). Culture has been the dominant mechanism by which humans have adapted to plants, often with major ramifications on various human and plant biological processes.

Cultural innovations made 2 mya con-

tinue to influence our utilization of particular plant taxa. The oldest traces of humanly controlled or produced fire at Chesowanja-Chemoigut Formation (1.42 mya) and at Lake Baringo (2.0 to 1.5 mya) (Clark and Harris, 1985) are associated with developed Oldowan or Acheulean Industry used by *H. habilis*, *H. erectus*, and possibly *Paranthropus*. The control of fire and its use in the detoxification of plant allelochemicals has made inedible foods edible. For example, there are a number of compounds present in the cultivated soybean (*Glycine max*) that have a negative impact on the quality of the plant's protein. Heat destroys the protease inhibitors and lectins inhibitors that otherwise would adversely affect the integrity of the pancreas and intestinal mucosa. However heat is less effective against the plant's goitrogens, tannins, phytoestrogens, saponins, and flatus-producing oligosaccharides (Liener, 1994) and consumers have had to develop alternative strategies to minimize the negative impact of ingesting these compounds.

Aside from the use of plants as sources of food and medicine, one of the earliest uses of plants by bands of gathering humans may have been the application of plants as bioindicators of ecological status. Specifically, the visual appearance of plants, in combination with the presence of particular key species or assemblages, can provide clues to the contamination status of nearby water sources and adjacent plants and animals (Gregson et al., 1994).

Within only the last 15,000 years, humanity has shifted from exclusive gathering and hunting to horticulture, and then to agriculture as the dominant occupational niche. The gradual, cross-cultural, worldwide transition to agriculture did not diminish the importance of plant-based foods for humans. In fact, some would argue that the transition intensified the interactive process (cf. Rindos, 1984) and, in certain settings, provided an excellent ecological context within which highly intense, locally restricted human-plant specializations could emerge. The transition to agriculture has been associated with phenotypic and genotypic changes in specific plant taxa, increased human and domesticated plant population numbers,

greater mutual reliance between local plant and human communities for survival, and in humans, restrictions in dietary breadth. Specific combinations of cultivated plants came to dominate particular cultural groups (e.g., maize [*Zea mays*] and common bean [*Phaseolus vulgaris*] in Central America) and local human groups inadvertently or intentionally concentrated their exposures to specific plant allelochemicals.

As human groups expanded their numbers in conjunction with the transition to agriculture and yet became more sedentary, their repertoire of knowledge about and access to diverse plants, especially wild plants, diminished. However, the depth of their knowledge about specific cultivated plants increased (cf., Navarez-Sandoval, 1995). Knowledge of the bioactive properties of these plants, particularly the potential medicinal properties of local domesticated plants, became even more valued as infectious diseases increased in sedentary groups. Many plants contain substances that are profoundly bioactive in humans. For example, melatonin, the chief hormone of the pineal gland in vertebrates, synchronizes circannual and circadian rhythms, inhibits cancer progression and promotion, stimulates immune system function, and scavenges free-oxygen radicals. This hormone has been found in high levels in certain edible plants (Dubbels et al., 1995). In a second example, licorice (*Glycyrrhiza glabra*) also contains plant-derived compounds with hormone-like activity in humans. One of the medicinal benefits of this ancient and broadly used legume root extract is its ability to inhibit 15-hydroxyprostaglandin dehydrogenase. Inhibition of this enzyme by a plant compound increases human prostaglandin levels, promoting the healing of ulcers (Baker, 1994).

There is some evidence that during the transition to agriculture, certain human groups may have inadvertently (and at times intentionally) selected more toxic plant varieties for domestication and consumption. For example, among indigenous Tukanoan peoples in the Amazon Basin, Dufour (1993) reports that the so called "bitter" cultivars of cassava (*Manihot esculenta*) are preferentially cultivated over the "sweet" cultivars of this important staple. Tukanoan reliance on

the more toxic varieties of their dietary staple is apparently a function of group culinary (taste and texture) preferences. The desired plant characteristics happen to also be highly correlated with the amount of cyanogenic glucoside in the root. Human selection (or tolerance) of plant varieties with more toxic properties may reflect human physiological flexibility afforded by the biocultural process. Humans, like other mammalian species and most insects, have developed elaborate detoxication systems to endogenously neutralize or at least reduce in toxicity ingested plant allelochemicals. However, in addition to these physiological defenses, humans have developed elaborate, culturally mediated, detoxification systems as well. Together, human metabolic detoxication and technological detoxification processes raise the tolerance threshold to plant toxicity.

#### **Plant toxicity and human strategies against plant defenses**

Plants have long been regarded as chemical arsenals. Research on mammalian herbivore-plant interactions led Freedland (1991) to identify two types of allelochemicals, based upon their modus operandi within the consumer. These two types are quantitative allelochemicals and qualitative allelochemicals as depicted in Figure 1.

Quantitative allelochemicals are often toxic at fairly low concentrations and after short periods of exposure. Frequently these compounds also have the side effect of being antinutrients (i.e., interfering with the digestion or assimilation of nutrients). Many medicines (and plants with medicinal properties) fall within the quantitative allelochemical category and have toxicities that are essentially dose independent. In fact, within this category, "food" grades into "medicine" very easily. Human consumption of large volumes of plants with these properties tends to be limited and toxicity is generally frequency independent.

Qualitative allelochemicals are toxic only after being consumed in high volume (evidencing dose dependent toxicity) or after prolonged exposure (evidencing frequency dependent toxicity). Threshold effects for qualitative allelochemicals are defined by

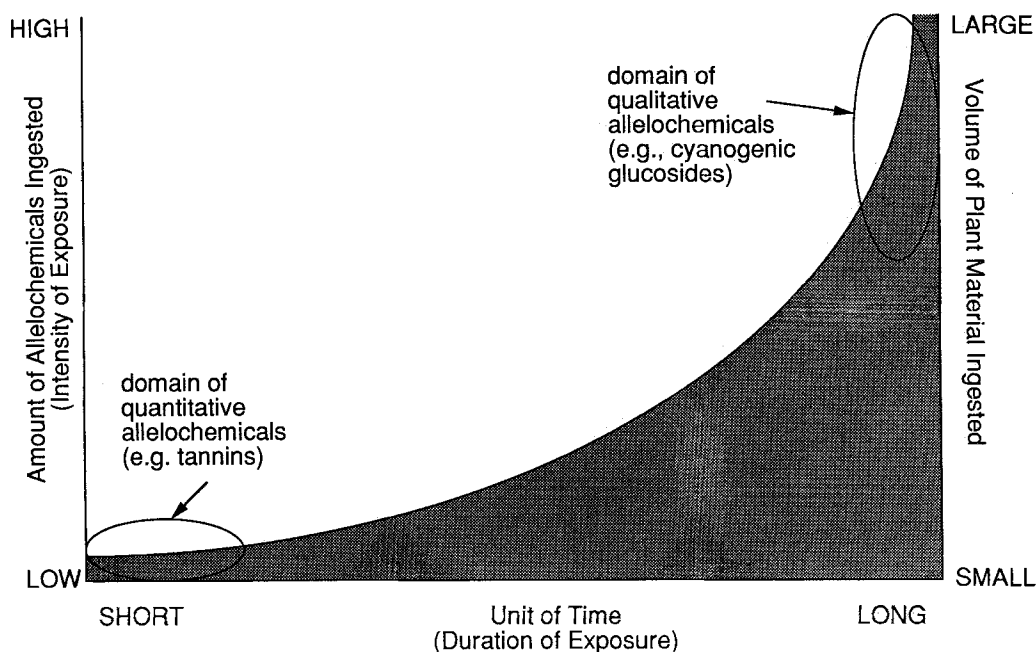


Fig. 1. Dosage intensity, exposure duration, and volume characteristics of quantitative and qualitative allelochemicals (from Jackson, 1996).

certain characteristics of the consumer (e.g., prior physiological state, body size). Consumption of plant based foods that retain toxic qualitative allelochemicals may be initially limited by the presence of other allelochemicals (i.e., multiple dietary toxins) that interfere with the final overall toxicity levels. Qualitative allelochemicals tend to exhibit threshold effects that are correlated with the role of the plant compound within the context of the total diet. For example, saponins and tannins consumed simultaneously or within a short time of each other provide detoxicant complementarity, that is, the saponins interfere with tannin toxicity and vice versa.

#### Characteristics of human-plant interactions

Most mammal-plant relationships are not the tightly fit reciprocal gene-for-gene interactions that represent one extreme of the coevolutionary spectrum. This is even more true for the special case of human-plant interactions. Humans are basically generalist feeders although local and regional variation is evident. When human diets are classed by

species, certain combinations of plants tend to dominate certain culture groups. In general the more specific the interaction, the more likely a coevolutionary interaction exists. Specificity is superimposed upon our generalism. Specialization to dietary plant toxins in humans is expressed at two levels: 1) at postprocessing levels where residual concentrations of bioactive allelochemicals may persist, reflecting the efficiency of the detoxification process, and 2) at the level of actual consumption where the mode of ingestion, that is, how the food product is actually eaten and what it is eaten with, will influence the rate of detoxication. Table 1 lists the central points to be considered in identifying the characteristics of human-plant interactions.

Human dietary specialization is influenced by a number of factors. Among the most important include: 1) access to alternative foods as a function of ecological and economic variables; 2) the baseline physiological status of the human group; and 3) the degree of nutritional precision in the diets of specific culture groups allowing them to

TABLE 1. Key characteristics of human-plant interactions

- Virtually all plants, including those domesticated by humans, contain bioactive allelochemicals.
- These allelochemicals have dosage dependent toxic properties on their human consumers.
- These toxic properties play a major role in the identification and use of plant-based foods by humans.
- Humans, through their cultural innovations, mix and modify plant food products prior to consumption to maximize palatability, nutritional content, and desired physiochemical effect, and to minimize undesired toxicity and adverse effects. Plant toxicity mandates dietary diversity.
- Human physiology and food-related behavior has been selected, throughout our species long history as gathers and hunters, to seek out and store excess calories.
- Humans have been able to ingest greater quantities of food by mixing and physiochemically modifying food products prior to consumption.
- Humans cannot achieve high levels of plant food intake by ingesting any (random) selection of food plants—there has to be some level of specialization to particular combinations of allelochemicals.

Modified from Freedland, 1991.

recognize a correlation between a particular plant, its toxin loads, and their health status. This last factor, the cognitive awareness of the relationship between a particular pattern of plant ingestion and the expression of physiochemical symptoms in consumers, is often difficult, particularly with plants exhibiting qualitative allelochemicals.

Human tolerance for plant-derived toxins provides insights into possible specializations. Large mammals, such as humans, tend to be generally more tolerant to plant allelochemicals and their toxic metabolites. Hence identifying evidence for human adaptation and potential coevolution is more complex. However, in cases where we see any deviation from the usual capacity to process and/or tolerate particular plant metabolites, further study is warranted. Indeed, a higher than usual tolerance may provide some evidence of human adaptation while a lower than usual tolerance may signal an increased vulnerability. These "unexpected observations" are important signals (Fig. 2) for further investigation.

### Human geographical mosaicism and human-plant diversity

Exposure to plant allelochemicals, particularly compounds with clear deleterious effects on consumers, can be thought of as sources of environmental stress. Humans would be expected to respond to such plant-

derived stress with behavioral, physiological or morphological adjustments to counter these effects and maintain normal functioning. However, variation in the ability of individuals to respond to this stress could reflect diversity in genetic variation for plasticity of a stress response and/or genetic variation for the response itself (Hoffmann and Parsons, 1994). Geographical (i.e., spatial) heterogeneity in response to a particular constellation of plant allelochemicals may indicate genetic variation for stress responses within exposed humans.

Thompson (1994) developed and discussed the concept of geographical mosaicism as a reflection of coevolutionary specializations. Many aspects of this concept can be appropriately applied to the reciprocal interactions of humans and domesticated plants. Since modern humans are a single subspecies, all variations related to human-plant interactions are within-population events. Multispecies interactions can initiate and sustain variation below the subspecies level. When these interactions are most intense, local specializations can be of local microevolutionary significance and can contribute to the patterning of overall human diversification. Even when these interactions are superficial, they can produce discordant variations or "bumps" in clinal gradients when human biodiversity is viewed over geographical space. A plant-pathogen model developed by Frank (1991) analyzing the forces maintaining genetic polymorphism between coevolved interacting species found that ecological and demographic factors often have a more profound effect on the amount of polymorphism than genetic parameters. This conclusion may also be of relevance for humans and their domesticated plants. Human geographical mosaicism in response to human-plant interactions is sustained through the differential survival of consumers. This differential survival then contributes to the ultimate topography of human variation.

### CASE STUDIES

#### Human-plant diads

Interactions between humans and domesticated plants in the following two cases suggest that plant product use evokes differential physiochemical responses in consumers,

		Modified Plant Biology and Chemistry	
		Are bioactive allelochemicals present in the plant food and does the mode of ingestion facilitate physiochemical exposure to these allelochemicals?	
		YES	NO
Altered Human Biology and Culture	Do human consumers exhibit behavioral, physiochemical, or morphological change?	YES	NO
		expected observation	unexpected observation
	NO	unexpected observation	expected observation

Fig. 2. Two-by-two contingency table classified by presence and response to plant allelochemicals.

frequently with implications for the subsequent development of disease. Human-plant diads can thus demarcate a cultural group into those who have an antagonistic response and those who are able to develop a beneficial interaction with specific plant compounds.

#### East Asian ethnic groups and *Camellia sinensis*

Black, green, and Oolong tea all come from one plant, *Camellia sinensis*. Tea is broadly consumed with especially high intakes in East and South Asia, the British Isles, the Arabian Gulf States, and North Africa (Graham, 1992). The oldest report of tea domestication and use comes from China approximately 5000 BP, where tea was initially considered a medicine; it then became a social beverage, and ultimately the center of a cultural ritual (The Republic of Tea, 1993).

The major chemical constituents of tea are phenolic compounds, amino acids, and caffeine (Salunkhe et al., 1989). Polyphenols are the major allelochemical constituents of

young tea leaves. During the tea fermentation process, these phenolic compounds are oxidized. The major polyphenolics in black tea are theaflavins and thearubigins. These compounds interact with caffeine, reducing the toxicity of the latter compound (Salunkhe et al., 1989).

Tea is an important source of polyphenolic oxidants (for example flavonoids and tannins). Flavan-3-ol-tannins are known to be efficient scavengers of free radicals and important inhibitors of lipid peroxidation. Osawa (1992), Stich (1992), Ho and colleagues (1992, 1994), Chung et al. (1993), Li and colleagues (1994), Honda (1994), Kim et al. (1994), and Salah and colleagues (1995) are among the many authors who have written extensively on the antiproliferative effects of flavonoids in tea on cancer, suggesting that they can entrap genotoxic agents and hence inhibit the spread of cancer. Other researches have indicated that tea polyphenols can also inhibit the inflammatory dermatoses and immunosuppressive effects of ultra-



violet B (UVB) radiation (Conney et al., 1992; Agarwal et al., 1993; Katiyar et al., 1995).

Tea has a number of other beneficial physiochemical effects on humans as well (Hara, 1994). It is mildly stimulatory, provides essential minerals and vitamins, and probably has a therapeutic value in the prevention of dental caries. It is useful in the treatment of vascular and coronary disorders, including atherosclerosis. For example, tea-derived flavonoids have been suggested to have a protective effect against coronary heart disease among elderly men in the Netherlands (Hertog et al., 1993). Tea has also been reported to be a digestive aid and to stimulate peristalsis. Tea allelochemicals reportedly also inhibit influenza virus infection (Shimamura, 1994) and HIV-reverse transcriptase (Nakane et al., 1994).

On the negative side, however, is the potential for tea-derived polyphenols to precipitate proteins, interfere with the availability of other dietary nutrients, and promote esophageal cancer. Polyphenols constitute nearly half of the total solids in a cup of tea. Whether or not these plant compounds behave in vivo as true tannins and form stable complexes with human proteins is currently under investigation. Butler and colleagues (1987) report that increased amounts of unique salivary proline-rich proteins (PRPs) are produced with a very high affinity for polyphenols. The astringency of tea is likely due to the interaction of salivary proteins in the mouth with *Camellia sinensis* polyphenols. In humans these PRPs constitute an adaptive response to dietary polyphenols and related phenolics and, by binding to them, complexes are able to minimize their antinutrient effects (Haslam, 1993). Dietary phenols also increase the weight of the parotid gland, the site of increased salivary protein excretion. These physiological changes in tea consumers may serve as important adaptive responses to the deleterious effects of these allelochemicals. Figure 3 summarizes many of the bioactive effects of tea.

#### **North Atlantic European ethnic groups and *Triticum aestivum***

While wheat (*Triticum aestivum*) has a relatively long history of East Asia (Crawford, 1992) and the Near East (Miller, 1992), in

Europe this crop was largely restricted to the southern and southeastern regions. Ecologically, Europe is highly diverse. In the northern and highland parts of Atlantic Europe (the British Isles, Norway, and much of Sweden and Denmark), the severity of the winters and the shortness of the growing season greatly constrain crop production (Dennell, 1992). Dietary staples in these regions tend traditionally to be barley and oats, rather than wheat.

In these same regions today, celiac disease attains its highest incidence and prevalence. The highest world prevalence of this immunological disorder is in western Ireland. Celiac disease is an expression of cell-mediated immunity that is triggered by ingestion of wheat gliadin, although as yet unknown compounds in rye, barley, oats, or triticale have also been suggested to provoke sensitivity in susceptible humans (Campbell, 1992). In wheat, plant proteins can bind to gliadin-specific T cells in the small intestines of patients with celiac disease (Lundkin et al., 1994) and initiate an abnormal immune response that is frequently life threatening.

The hypersensitivity of many members of North Atlantic European ethnic groups to wheat gliadins suggests limited past exposure to these plant-derived compounds. Simoons (1981) was among the early researchers to propose a relationship between the historical geographical patterns of wheat use and the associated patterns of HLA variation, although at that time the interest was in HLAB8 phenotypes and wheat lectins. Subsequent research now casts doubt on the lectin hypothesis, however (Ruhlmann et al., 1993). More recent studies using techniques from molecular biology have focused on the susceptibilities of various HLA-DQ phenotypes. Distinct alpha and gamma-type gliadins from wheat endosperm have been identified as celiac immunoreactive proteins (Rocher et al., 1995) in individuals with specific HLA-DQ phenotypes. Gliadin-specific T cells in the small intestinal mucosa of HLA-DQ2+, individuals are almost exclusively restricted by amino acids 31–49 (Sturges et al., 1994) (and possibly other amino acids) of the plant protein. HLA-DQ beta *I\*0201* is directly associated with sensitivity to wheat gliadins and attains its highest in-

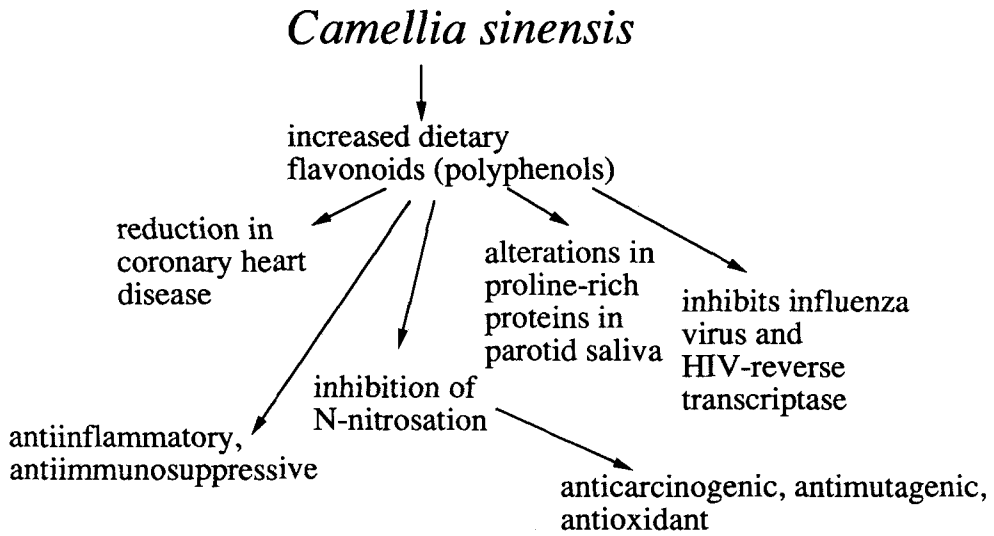


Fig. 3. Range of effects of *Camellia sinensis* allelochemicals in human consumers.

cidence among Northern Atlantic European ethnic groups. Figure 4 outlines these relationships.

#### Human-plant-parasite triads

Frequently, established human-plant diads are attractive to the involvement of a third species. Interactions between humans, their domesticated plants, and a parasitic protozoa in the next two cases suggest that plant product use can initiate differential physiochemical responses both in consumers and in other organisms normally pathogenic for these consumers. In this sense, the presence of the plant compounds can influence the course of infection and the expression of human disease. Human-plant-parasite triads are among the most convincing cases for human-plant coevolution. As in human-plant diads, the interactions of a triad can partition a cultural group into those who have an antagonistic response to the third species in the presence of specific plant compounds and those who are able to beneficially incorporate exposure to specific plant compounds in their response to the presence of a third interacting species. In the two triad case studies presented below, the third interacting species in each case is *Plasmodium falciparum*, causative agent of falciparum

malaria and the most important infectious disease in human history.

#### Circum-Mediterranean ethnic groups, *Vicia faba*, and *Plasmodium falciparum*

The circum-Mediterranean area is ecologically easy to demarcate and has been a region of extensive and ancient transhumance. In this region, fava beans (*Vicia faba*), also known as broad beans, have long been cultivated and they are one of the most important and widely consumed pulse crops among circum-Mediterranean peoples. Fava beans are an excellent source of protein and have an amino acid balance that complements that of cereals. Domesticated *Vicia faba* has been reported as early as 8,600 years BP in the Levant (Kislev, 1985) and similarly dated *Vicia faba* has been found in Greece.

Fava beans also contain the toxic glycosides vicine and convicine as well as relatively low concentrations of several other antimetabolites (Marquardt, 1989; Burbano et al., 1995). Under certain conditions and in certain susceptible individuals, the consumption of fava beans and exposure to the glycosides vicine and convicine (and their aglycones divicine and isouramil) produces an acute hemolytic anemia, a metabolic disease known as favism.

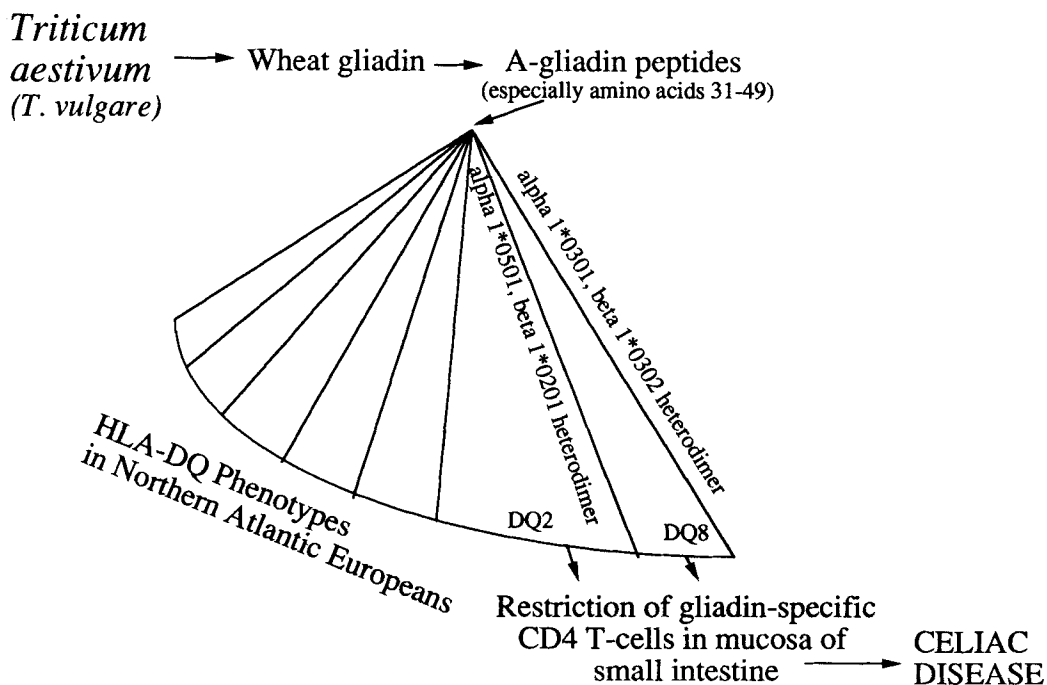


Fig. 4. Relationships of wheat gliadin and HLA-DQ phenotypes in Northern Atlantic European peoples.

Favism has been recognized since antiquity among circum-Mediterranean peoples. The disease is frequently lethal, especially in boys (see Rieple et al., 1993, for a classic study in a young Greek). Low enzyme activity levels of the red blood cell enzyme glucose-6-phosphate dehydrogenase (G6PD) is the most consistent finding among susceptibles. Specifically, the Gd<sup>med</sup> variant of G6PD, or a biochemically similar genetic variant, is involved in the expression of this disease. Gd<sup>med</sup>-like variants include Gd<sup>Ferrara I</sup>, Gd<sup>A-</sup>, and Gd<sup>Matera</sup>. Each of these variants is the result of a guanine to adenine mutation at nucleotide 202 in exon IV (causing a valine to methionine amino acid substitution) and an adenine to guanine mutation at nucleotide 376 in exon V (causing an asparagine to aspartic acid amino acid substitution) (Cappellini et al., 1994). A large number of G6PD variants exist with reduced enzyme activity (Hirono and Miwa, 1993). In fact, G6PD diversity has been identified as the most widespread polymorphism in humans.

When individuals with less than 5% of normal G6PD activity come in physiological contact with fava bean glycosides, they have the potential to develop favism (Galiano et al., 1990). G6PD deficiency and the potential for favism may also be related to individual differences in the characteristics of G6PD promoter regions (Rank et al., 1994; El-Hazmi et al., 1994; Phillippe et al., 1994). Ironically, favism-susceptible levels of G6PD are fairly commonly encountered among individuals from circum-Mediterranean ethnic groups, in spite of the long history of dietary contact with the plant's glycosides. It is in this biocultural irony that a role for a third species, *Plasmodium falciparum*, emerges.

*Falciparum malaria* is the most severe of the human malarias, most widely distributed, and hence most important clinical and epidemiological form of malaria. In vitro studies of this parasite indicate that the growth and development of *Plasmodium falciparum* is significantly inhibited in G6PD-deficient red blood cells that have been

treated with the favism-inducing agent isouramil (Golenser et al., 1983). Similar inhibition does not occur in G6PD-adequate red cell treated with isouramil. Divicine has also been shown to inhibit *P. falciparum* parasite development in an animal model.

When a culture group maintains exposure to a group of plant compounds that are clearly harmful to a discernible proportion of the population, researchers can be fairly confident that something else is going on. Apparently that something else, in the triad of G6PD, fava beans, and falciparum malaria, is increased protection against the morbidity and mortality associated with malaria infection. Figure 5 depicts the interrelationships in this triad. It is worth noting that a similar triad has been proposed by Kitayaporn and colleagues (1992) for Hb $\beta$ E, *Vicia faba*, and *Plasmodium falciparum* among Southeast Asian ethnic groups. Hb $\beta$ E is commonly encountered among lowland Thai.

#### **West African ethnic groups, *Manihot esculenta*, and *Plasmodium falciparum***

Cassava (*Manihot esculenta*) is a pantropical perennial shrub original domesticated in the American tropics (northeastern Brazil, Mesoamerica, and Venezuela). Dessicated plant remains identified as cassava and dated 2,500 years BP have been found in Mexico (Rogers, 1965). Plant remains from the central coast of Peru have been dated as early as 10,000 years BP (Engel, 1973). Cultivated cassava was selected for large roots, more erect and less-branched above-ground growth, and asexual propagation from stalk cuttings (Jennings, 1976). These morphological characteristics and the importance of cassava as a carbohydrate source contributed to its transport to and acceptance in West Africa by 400 years BP. Here, among many ethnic groups of the tropical rainforest and wet savanna, cassava supplanted yam (*Discorea* spp.) cultivation and use. Cassava is now the most important root and tuber carbohydrate staple in Africa as well as an important leaf vegetable addition to many traditional cuisines.

*Manihot esculenta* is among the most significant food sources of biological cyanide. Cassava contains the cyanogenic glucoside compounds linamarin and lotustralin. Once

ingested, these compounds are metabolized to thiocyanate and cyanate, which are also biologically active although less toxic than cyanide.

West Africa is an area where the gene frequency for Hb $\beta$ S is fairly high and falciparum malaria is hyperendemic. In vivo, dietary derived cyanide compounds are able to irreversibly carbamylate the NH-terminal end of the  $\beta$ -globin chain (Jackson et al., 1988). This chemical modification of the  $\beta$ -globin chain of hemoglobin has important implications on subsequent hemoglobin structure and function. In individuals with Hb $\beta$ S, this has the effect of inhibiting sickling, increasing Hb $\beta$ S oxygen-carrying abilities, and slightly extending the lifespan of Hb $\beta$ S-containing red blood cells. At levels of expected dietary intake, cyanide-related compounds (such as cyanate) are also able to modify essential proteins of *Plasmodium falciparum* and inhibit parasite survival (Nagel et al., 1980). Physiological levels of these same compounds can reduce human G6PD activity levels as well (Glader and Conrad, 1972). It has been proposed, on the basis of field and laboratory evidence, that when plant ingestion volumes are large and human exposure to cyanogenic glucosides consistently high, plant allelochemicals *directly interact* with invading *P. falciparum* parasites and inhibit their growth and development (Jackson, 1990). This pattern of human-plant-parasite contact may decrease Hb $\beta$ S gene frequencies within a cultural group over time as plant allelochemicals supplant the *Plasmodium*-retarding effects of Hb $\beta$ S. In this model, human and parasite exposures to cassava-derived compounds would reduce the selective advantage of Hb $\beta$ S, and lower sickle cell gene frequencies over time. When plant ingestion volumes are small or intakes are seasonal, plant chemicals would tend to improve the biological fitness of individuals homozygous for Hb $\beta$ S and thus elevate sickle cell gene frequencies. At these lower levels of human exposure to plant allelochemicals, intakes would be neither consistent nor high enough to thwart year-round in vivo *P. falciparum* proliferation and growth. The impact of the plant on the human-parasite interaction is therefore dosage dependent. Within the hyperendemic malarious environment of West Africa, cas-

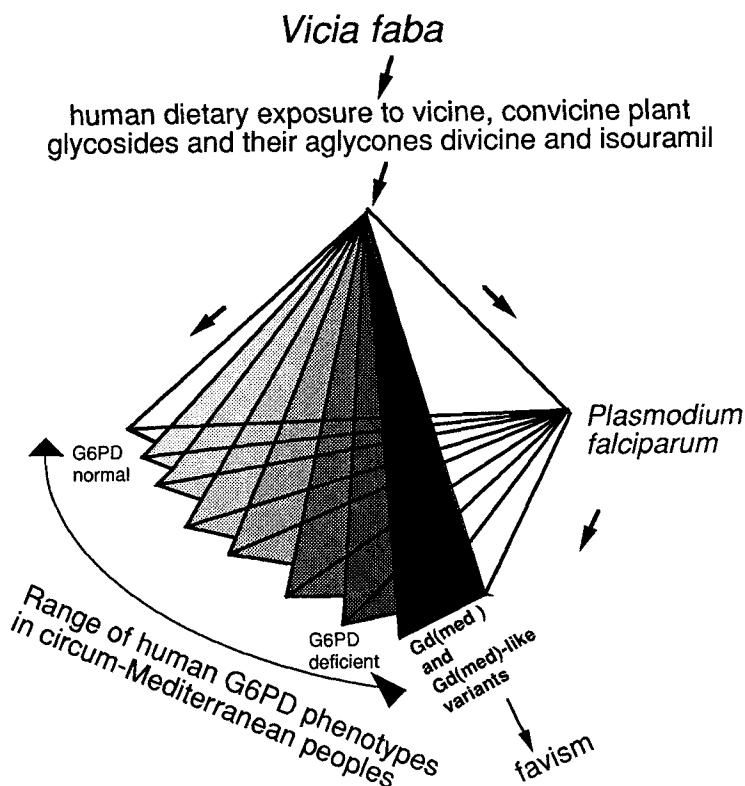


Fig. 5. Effects of exposure to *Vicia faba* allelochemicals on human G6PD phenotypes and *P. falciparum* in circum-Mediterranean regions.

sava-derived dietary allelochemicals may modulate the gene frequency of Hb $\beta$ S, producing localized punctuated microevolution. Figure 6 depicts the coevolutionary triad-related human metabolic effects associated with exposure to *Manihot esculenta* cyanogenic glucosides.

It is worth noting that compounds from other domesticated plants have also been proposed to have antisickling activity against Hb $\beta$ S. Activated ester derivatives of hydroxybenzoic acid have been cited as potential antisickling agents (Lamba et al., 1990). Such compounds have been identified in pigeon pea (*Canjanus cajan*) (Akojie and Fung, 1992), an annual legume of African origin that is a particularly important crop in the semiarid tropical regions of India, Africa, and the Caribbean (Martin, 1984).

## CONCLUSIONS

From this discussion it is clear that the presence of bioactive allelochemicals in most plants, particularly those selected for domestication and consumption, blur the distinction between "food" and "medicine." Many domesticated plants retain bioactive allelochemicals of clear pharmacological import. In certain ecological and sociocultural contexts the relationship between specific humans and specific plants is indeed coevolutionary in the sense that the gene products of each group influences the biological fitness (i.e., survival value) of the other. This reciprocal influence of nonoverlapping gene pools infers that human biology and behavior modulate and are modulated by plant biology and chemistry. When a third species is introduced to human-plant diads, plant

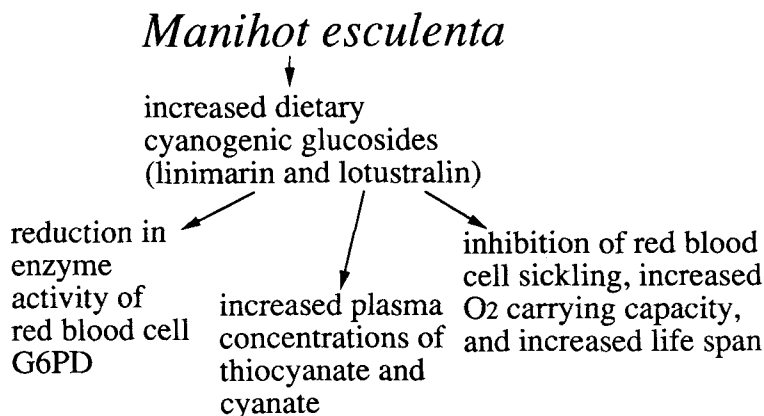


Fig. 6. Some human metabolic effects of dietary cyanogenic glucosides.

products may assist humans in the regulation of this species as well.

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